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DINÂMICA FISIOLÓGICA DA VARIABILIDADE CARDÍACA: UMA ABORDAGEM ESTATÍSTICA NA SÍNCOPE VASOVAGAL

PHYSIOLOGICAL DYNAMICS OF HEART RATE VARIABILITY: A STATISTICAL MODELING APPROACH IN VASOVAGAL SYNCOPE

DINÁMICA FISIOLÓGICA DE LA VARIABILIDAD CARDIACA: UN ENFOQUE ESTADÍSTICO EN LA SINCOPE VASOVAGAL

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RESUMO

Introdução: A perda transitória da consciência e tónus postural seguido de rápida recuperação é definida como síncope. Tem sido dada atenção a uma síncope de origem central com descida da pressão sistémica conhecida por síncope vasovagal (SVV).

Objetivos: A análise da variabilidade da frequência cardíaca (HRV) é uma das principais estratégias para estudar a SVV através de protocolos padrão (por exemplo tilt test). O principal objetivo deste trabalho é compreender a importância relativa de diversas variáveis, tais como pressão arterial diastólica e sistólica, (dBP) e (sBP), volume sistólico (SV) e resistência periférica total (TPR) na HRV.

Métodos: Foram usados modelos estatísticos mistos para modelar o comportamento das variáveis acima descritas na HRV. Analisaram-se mais de mil e quinhentas observações de quatro pacientes com SVV, previamente testados com análise espectral clássica para a fase basal (LF/HF=3.01) e fases de tilt (LF/HF=0.64), indicando uma predominância vagal no período tilt.

Resultados: O modelo 1 revelou o papel importante da dBP e uma baixa influência de SV, na fase de tilt, relativos à HRV. No modelo 2 a TPR revelou uma baixa influência na HRV na fase de tilt entre os pacientes.

Conclusões: Verificou-se que a HRV é influenciada por um conjunto de variáveis fisiológicas, cuja contribuição individual pode ser usada para compreender as flutuações cardíacas. O uso de modelos estatísticos salientou a importância de estudar o papel da dBP e SV na SVV.

Palavras-chave: síncope vasovagal; frequência cardíaca; modelos mistos.

ABSTRACT

Introduction: The transitory loss of conscience and postural tone followed by rapid recovery is defined as syncope. Recently has been given attention to a central mediated syncope with drop of systemic pressure, a condition known as vasovagal syncope (VVS).

Objectives: The analysis of Heart Rate Variability (HRV) is one of the main strategies to study VVS during standard protocols (e.g. Tilt Test). The main objective in this work is to understand the relative power of several physiological variables - Diastolic and Systolic Blood Pressure, (dBP) and (sBP), Stroke Volume (SV) and Total Peripheral Resistance (TPR) in Heart Rate Variability (HRV) signal.

Methods: Statistical mixed models were used to model the behavior of the above variables in HRV. Data with more than one thousand and five hundred observations from four patients with VVS were used and previously tested with classical spectral analysis for basal (LF/HF=3.01) and tilt phases (LF/HF=0.64), indicating a vagal predominance in the tilt period.

Results: Statistical models reveal, in Model 1, a major role in dBP and a low influence from SV, in the tilt phase, concerning HRV. In Model 2 TPR disclose a low HRV influence in the tilt phase among VVS patients.

Conclusions: HRV is influenced by a set of physiological variables, whose individual contribution can be assessed to understand heart rate fluctuations. In this work, the use of statistical models put forward the importance of studying the role of dBP and SV in VVS.

Keywords: vasovagal syncope; heart rate; mixed models.

RESUMEN

Introducción: La pérdida transitoria de la conciencia y tono postural, seguido de rápida recuperación se define como el síncope. Se ha prestado atención a un síncope acompañado por la disminución de la presión sistémica, conocida como síncope vasovagal (SVV).

Objetivos: El análisis de la variabilidad del ritmo cardíaco (HRV) es una estrategia para estudiar la SVV durante protocolos estândar (por ejemplo, tilt test). El objetivo de este trabajo es comprender la importancia de las diversas variables - presión diastólica y sistólica (dBP) y (sBP), el volumen sistólico (SV) y la resistencia periférica total (TPR) en la variabilidad de la señal de la frecuencia cardíaca (HRV).

Métodos: Se utilizaron modelos estadísticos para modelar el comportamiento de las variables descritas en HRV. Datos de más de mil quinientos observaciones de cuatro pacientes con SVV fueron utilizados y probados previamente con el análisis espectral clásico para el periodo basal (LF/HF=3.01) y del tilt (LF/HF=0.64), lo que indica una predominio vagal en el período tilt.

Resultados: El modelo 1 reveló un papel importante de la DBP y la disminuida influencia del SV en el tilt. En modelo 2, TPR ha mostrado una baja influencia de la HRV en la fase tilt.

Conclusiones: Se ha encontrado que HRV es influenciada por un número de variables, cuya contribución individual se puede utilizar para entender sus fluctuaciones. Los modelos han destacado la importancia de estudiar el papel de dBP y SV en la SVV.

Palabras Clave: síncope vasovagal; frecuencia cardíaca; modelos mixtos.

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INTRODUCTION

Syncope is defined as a transient loss of conscientious and postural tone which is followed by a rapid onset. Syncope episodes present high incidence (Aydin, Salukhe, Wilke, & Willems, 2010) being an important cause of medical concerns. One of the main classifications of syncope is the division among benign syncope from other types whose origin is from functional causes. A pathophysiological classification of syncope according to the 2009 guidelines of the European Society of Cardiology (Moya et al., 2009) presented three main causes as origin of syncope. The Reflex syncope (or neural mediated) where it is included the vasovagal syncope (VVS), but also carotid sinus syncope or atypical forms; The orthostatic hypotension cause, including primary and secondary Automonic failures (Parkinson disease and Diabetes Mellitus) and volume depletion causes; and Cardiac Syncope in which the origin is related with arrhythmias or structural diseases (such as myocardial infarction). Causes of VVS still present a challenge for clinical research usually being preceded by symptoms of autonomic activation (pallor, nausea and sweating), and is typically known as “common fainting”.

Among reflex syncope the vasovagal type is the most common cause in young patients, revealing a peak incidence between 10 to 30 years (Ganzeboom, Colman, R eitsma, Shen, & Wieling, 2003).

The head-up tilt-table (HUTT) test is used to assess the regulatory response of posture changes, a provocative maneuver to activate homeostasis.

In this work, the aim is to analyze HRV (Heart Rate Variability) signal obtained during HUTT protocols and the power of Diastolic Blood Preasure (dBP), Systolic Blood Pressure (sBP), Stroke Volume (SV) and Total Peripheral Resistance Index (TPR) to explain the influence of each variable with the proposed statistical mixed model. These models will guide the clinical management in VVS by centering the action in the most important variables.

1. THEORETICAL FRAMEWORK

HUTT is a clinical test thought to exaggerate the pathogenesis of the neurocardiogenic syncope. The patient is placed in a tilting bed (with foot support) ranging from 0 to 80 degrees (depending on the model and trade mark). During tilt movement, and by the influence of the gravity, the blood moves to the lower extremities, thus decreasing pre-load sensed by the non-myelinated C fibers in the wall of the left ventricle. This information is sent to the nervous system and used to increase the sympathetic outflow (Ljilja, Mišmaš, Adamec, & Habek, 2013) slightly increasing diastolic blood pressure and heart rate. The tilt table apparatus simulates the position change (from decubitus from upright position), thus forcing the reduction in pre-load, which is reinforced by the absence on the muscle contraction of lower extremities muscles. By this way, this provocative maneuver exaggerates the neurocardiogenic syncope conditions, and is used as a clinical test in VVS.

Although HUTT test has been used for more than 60 years, the absence of gold standard protocols is a major drawback concerning sensitivity and specificity levels of diagnosis. Tests with normal volunteers and with patients who had history of VVS, present 90% of specificity and sensitivity ranging from 32% and 82% (Parry & Kenny, 1999b). Provocative additional tests (e.g. carotid sinus massage or the use of pharmacological vasodilatation) may increase sensitivity values (Ljilja et al., 2013; Parry & Kenny, 1999b).

The physiopathological questions around VVS still founds a challenge for clinical research, and the use of statistical mixed linear methods are suitable to establish mathematical models to disclose the importance of standard physiological variables to explain the HRV signal dynamics.

2. METHODS

To derive the statistical models, data obtained during the HUTT test were selected. For each patient, one period of the basal phase (dorsal decubitus) of the test with five minute length was selected, and another period in the tilt phase with the same duration was also elected. Data with more than one thousand and five hundred observations from four patients with VVS (two males and two females) were randomly selected from the clinical file of disautonomia consultation, with clinical indication to tilt maneuver diagnosis test. These data were used also in the context of other clinical study whose details can be found in (R. Fonseca-Pinto, Ducla-Soares, Araújo, Aguiar, & Andrade, 2009)fractional Gaussian noise (fGn.

For each period (named basal and tilt, respectively) HRV signal was derived after the processing of ECG (second derivation) by extracting the time instants of R waves and setting the time between R waves. The graphical plotting of this information is known as tachogram. This tachogram is then submitted to an interpolation algorithm by cubic splines, using a 4 Hz interpolation frequency. An example of a tachogram is presented in Figure 1 at the top, and the EKG from which the signal is derived at bottom.

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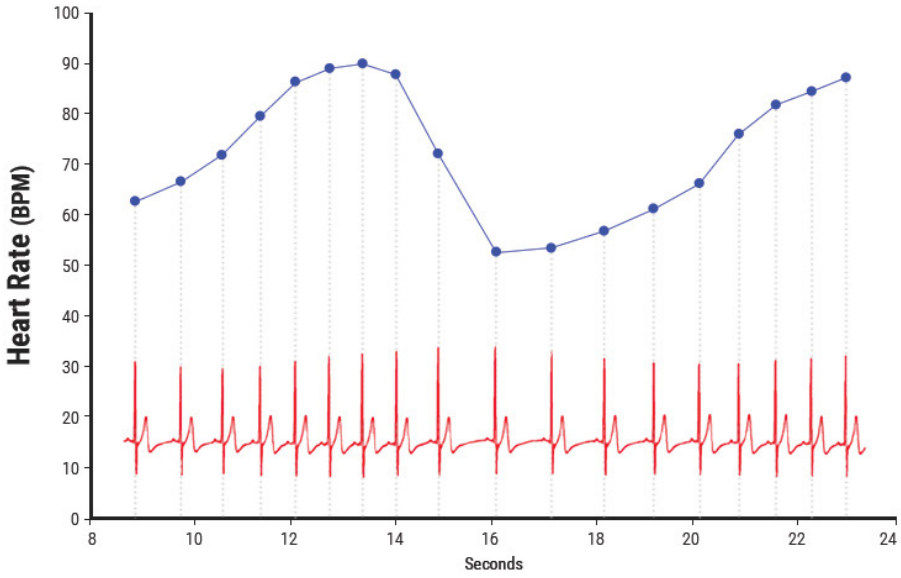

Figure 1 – Bottom- EKG with 18 R waves (in 15 seconds), and the derived tachogram (top). This figure was adapted from (McCraty & Royall, 2015)

The HVR signal is used to assess the cardiac reply to neural firing in response to changes to maintain homeostasis. In fact, back in 1963 in (Hon & Lee, 1963)exercise, and recovery heart rate are receiving increasing interest for monitoring fatigue, fitness and endurance performance responses, which has direct implications for adjusting training load (1 fetal distress was first reported to preceded changes in interbeat intervals, even before heart rate changes. Today there exist a variety of methods to assess the HRV pattern, ranging from the simple time-domain analysis to the new methodologies adapted to the non-linearity and non-stationarity of the physiological dynamics (Rui Fonseca-Pinto, 2011; Parry & Kenny, 1999b).

The methodology used to process HRV signal in this work was the spectral analysis via Kubios software (Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2014), using the Power Spectral Density (PSD) graph to derive the Sympathovagal Balance (SVB) as the quotient between Low Frequency (LF) band ranging from 0.05 Hz to 0.15 Hz; and the High Frequency (HF) band from 0.15 Hz to 0.4Hz of normalized frequency. This autonomical spectral derived index is defined in Equation 1:

$$SVB = \frac{LF}{HF}. \quad \text{(Equation 1)}$$

As the HF power is a measure of the vagal outflow, in Equation 1 when the quotient is smaller than 1 and there is a parasympathetic dominance in the time period in study. In the reversal case, the sympathetic system supremacy denotes an index bigger than 1. In the present study, SVB index was calculated for each patient, both in the basal and also in the tilt phases. The use of HUTT test, in the context of this work, served to confirm VVS and objectively use data from patients with a certified and objective diagnosis.

Joint with HRV signal, other physiological variables were registered to be used in the statistical model. These variables (sBP, dBP, SV, TPR) belong to the standard protocol of HUTT test and his record does not interfere with the test.

In this study, statistical linear mixed models were used to model the behavior of the above identified variables in the HRV signal. In several cases (as in the case here), data are grouped with variable correlations in the same group. The use of models with fixed and random parameters to model this kind of data is a good option to the work presented among this study in VVS patients and HUTT test (Seco & Vieira, 2014). Models enrolling both effects (fixed and random) are known as mixed models, whose parameters can be linear or nonlinear.

Mixed models use random parameters to translate the dependency between variables whose observed values are grouped. Some fixed parameters are associated with common characteristics of the population and the random parameters represent individual characteristics of each group, or deviations regarding the general population characteristics. These models, developed mainly from the work of (Laird & Ware, 1982), have big potentiality, are flexible and are adequate for equilibrate and non-equilibrate data.

At computational level, and since the work of (Pinheiro & Bates, 2000) these models have significantly evolved, as they use efficient

algorithms, leading to trustful results. Due to its excellent implementation in R software (R Core Team, 2014), the *library nlme* were used in this work.

The details of the model are now presented:

Let be a vector with dimension , *i=1,...,M,* of observations grouped in *M* groups. When there is only one group, the model proposed by (Laird & Ware, 1982) is presented in Equation 2:

$$y_i = X_i\beta + Z_i b_i + \varepsilon_i \quad ,i=1,...,M, \quad ;$$
$$b_i \sim N(0,\Sigma), \ \varepsilon_i \sim N(0,\sigma^2 I), \qquad \text{(Equation 2)}$$

where β is a vector of fixed parameters (fixed effects) of dimension *p*, is a vector of random parameters (aleatory effects) of dimension *q*, e are matrix of the model of order ×*p* e ×q, respectively. The columns of are, in general, a subset from the columns of . is a vector of dimension , designated by «residual error» within groups.

It is assumed that and have Normal multivariate distribution N(0,Σ) and N(0,σ²I) respectively, independent for different *i's* (groups) and independent between themselves. Σ is the variance-covariance matrix.

The assumption that var() = σ²I, *i=1,...M*, can be generalized.

The mixed linear model can be regarded as an extension of the classic linear multivariate regression model, where an additional "error" is considered, traducing the correlations between observations bellowing to the same group (Seco, Felgueiras, Fdez-Riverola, & Pereira, 2011). The estimators from fixed parameters β are obtained from the likelihood function, and the variance components estimation is made using the restricted maximum likelihood method (REML).

3. RESULTS

The HUTT test was performed in all patients of the disautonomia consultation, and among them, 4 volunteers were randomly selected. The two five minute period (basal and tilt) were treated with spectral methods to obtain the SVB index defined in (Equation 1).

The mean of the SVB index for the basal period was thus indicating an increasing power of the low frequency, hence a bigger sympathetic prevalence. In the tilt phase, the sympathovagal index was , indicating an over activation of vagal system in this phase of the test. It is important to remind that, in physiological conditions the upright position simulated by the tilt should increase the sympathetic tone. This was not the case within these patients, and the HUTT test was positive for VVS.

In order to derive the mathematical model (in fact two models were presented in this work) more than one thousand and five hundred observations were collected for the two phases of the test. Joint with HRV also dBP, sBP, SV and TPR were collected.

Statistical mixed linear models (as described above) were used to model the behavior of the identified variables with clinical relevance. The main goal was to found a satisfactory model to translate the influence of dBP, sBP, SV and TPR in HRV, being the last one the response variable.

Data represent four groups (one for each patient) and it was considered a random parameter (random intercept) for each one, modeling the correlations between the registered observations for each individual, and also estimating the deviation observed regarding the global mean of the model.

This work put forward two models explaining HRV dynamics, one with 3 variables (SV, sBP and dBP) from now on designated by model 1, and another with four variables (SV, sBP, dBP and TPR), the model 2.

Regarding model 1 the power of each variable for the basal phase and also for the tilt phase can be found in Table 1. It is also possible to see, for each independent variable, the estimated standard errors in the second row and the random intercept in the last row.

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Table 1 – Statistical mixed model 1, for HRV in the two phases of the HUTT test. Estimates of each of the three variables in the model in the first raw for each of the two phases (basal and tilt).

		Intercept	SV	sBP	dBP
Basal	Model 1	5.812	-0.053	0.048	-0.127
	Standard error	2.43	0.06	0.02	0.02
	Standard deviation of random intercept			0.572	
Tilt	Model 1	14.982	-0.079	0.373	-0.743
	Standard error	9.79	0.06	0.1	0.16
	Standard deviation of random intercept			2.441	

To normalize the values obtained with the model in order to compare with others (in particular with different number and types of variables), the division by the intercept value was implemented. The results of the obtained normalized model can be found in Figure 2.

By the analysis of Figure 2, it is possible to perceive the importance of pressure changes in the HRV signal during the tilt phase. In fact, the tilt phase reinforces de contribution of sBP (in the same direction as in the basal phase) but also, and more significantly in the dBP signal, for which the variation is bigger. As in the systolic pressure, the increasing trend has the same direction. The SV do not have significant power in the HRV signal and in the case of the tilt phase it decreases his influence over HRV inputs. This is explained by the lacking in homeostatic response due to the VVS condition in these patients.

Another interesting result (offering pharmacological relevance) is related to information provided by the model regarding the use of adrenergic receptors in VVS management. In fact, one of the commonly used drugs in VVS are the β-adrenergic blockers, the first choice for many years, by reducing the initial sympathetic activation in the beginning of the syncope. However, the lacking of evidence of its use is pointed as a major risk to this practice (Parry & Kenny, 1999a). Despite the existence of several studies claiming positive results with β-blocker treatment in syncope (Parry & Kenny, 1999a), according to the European Society of Cardiology guidelines, β-blockers should not be used to treat reflex syncope (Moya et al., 2009) due to the absence of effectively proved benefit. Nevertheless, the results advanced by this model 1 are consistent with the use of β-adrenergic blockers. The increased power of systolic pressure in the tilt phase is a marker of sympathetic modulation, thus the use of β-adrenergic blockers are indicated to control this mechanism by reducing heart rate and hence systemic pressure. Regarding the negative exacerbation of dBP (thus decreasing his influence in the HRV signal) during the tilt phase it can be regarded as lacking of peripheral sympathetic response. This is the rational for the use of α-agonists to manage VVS, which is also supported by the model. Adrenergic α-receptors are located in the smooth muscle of the peripheral arteries, thus to balance the vasodilation in the tilt phase, the use of alpha adrenergic agonists can be activated to overcome the lacking of response and contribute to decrease headed syncope symptoms and its recurrence.

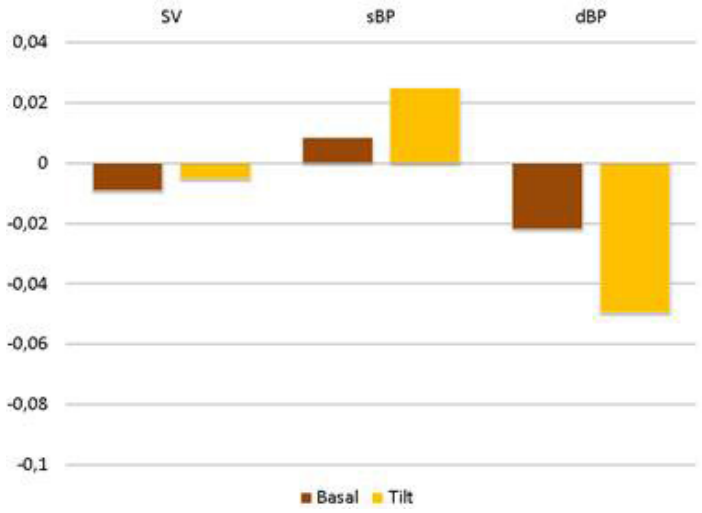

Figure 2 - Normalized model 1 for the basal and tilt period.

Alongside pressure values and stroke volume, another important variable mainly related with sympathetic system is the peripheral resistance (in fact total peripheral resistance, as an overall resistance to blood flow through the systemic blood vessels – TPR). Hence, a second model (model 2) including all the previous variables in model 1 and also TPR were considered.

In accordance with the previous results of model 1, values for the model are presented in Table 2 and the normalized version for comparison purposes was drawn in a bar graph in Figure 3.

Table 2 - Statistical mixed model 2, for HRV in the two phases of the HUTT test. Power of each of the three variables in the model in the first raw for each of the two phases (basal and tilt).

		Intercept	SV	sBP	dBP	TPR
Basal	Model 2	-6.001	0.556	-0.107	-0.113	0.004
	Standard error	3.00	0.09	0.03	0.03	0.00
	Standard deviation of random intercept			2.236		
Tilt	Model 2	13.065	0.101	0.150	-0.660	0.005
	Standard error	11.57	0.12	0.13	0.17	0.00
	Standard deviation of random intercept			4.581		

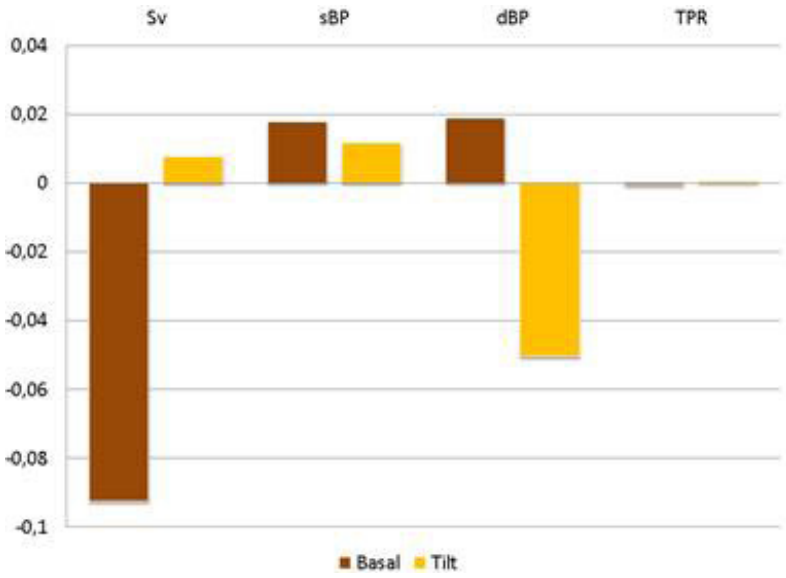

Figure 3 - Normalized model 2 for the basal and tilt period.

DISCUSSION

The inclusion of TPR in the model 2 denotes important changes in the power of the model variables, which is a mark of system complexity. The major changes occurred in SV and dBP. Regarding dBP, the values obtained in this model 2 for the tilt phase are coherent with the one from the previous discussed model 1, which implies more attention to the role of dBP management in patients with VVS and the ensuing use of α-adrenergic agonists to control vasodilation. Systolic Volume changes in model 2 reflect the introduction of TPR (as both variables contribute to the output value for the systemic pressure).

CONCLUSIONS

The mechanism of vasovagal syncope is incompletely understood and the overall dynamics of the main variables enrolled in his control were addressed in this work by the construction of two statistical models. As explained before, the lacking of consensus in the VVS management in particular regarding pharmacological targets is still a problem for which data analysis must be regarded as one more contribution. Results put forward in this work indicate the diastolic pressure as a target, but also a deeper understanding

of the relation between pressure and peripheral resistance.

Further work will include more patients and due to the underlying physiological nonlinearities in the process, the use of nonlinear statistical models.

CONFLICT OF INTERESTS

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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